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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,469	09/24/2001	Stephen J. Benkovic	6460-18-1	1582

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EXAMINER

FRONDA, CHRISTIAN L

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 02/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/868,469	Applicant(s) BENKOVIC ET AL.	
	Examiner Christian L. Fronda	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 November 2005.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-127 is/are pending in the application.
- 4a) Of the above claim(s) 12,13,41-52 and 90-127 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11,14-40 and 53-89 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 September 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. Claims 1-127 are pending in this application. Claims 12, 13, 41-52, and 90-127 have been previously withdrawn from consideration.
2. Claims 1-11, 14-40, and 53-89 are under consideration in this Office Action.
3. The rejection of claims 1-3, 7, 9-11, 14-40, and 53-89 under 35 U.S.C. 112, second paragraph, as being indefinite as being indefinite has been withdrawn in view of applicants' arguments and amendment to the claims.

Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
5. Claims 4-6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention
In claims 4-6 and 8, the phrase "corresponds to" renders the claim vague and indefinite because it is not clear if applicants are actually referring to the "naturally-occurring splint intein" or "Ssp DnaE". Amending the claims to recite that the intein is a "naturally-occurring splint intein" or a Ssp DnaE" may overcome the rejection.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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7. Claims 1-11, 14-40, and 53-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' arguments filed 11/18/2005 have been fully considered but are not persuasive. Applicants' position is that the inteins of the invention can be from any genus which applicants assert reflects the versatility of the invention; inteins RecA, DnaB, psp, Pol-I, or Pfu inteins are suitable in the methods of the invention; and that the common structural feature of each intein is the ability to be cleaved and reassemble. The examiner respectfully disagrees for reasons of record as supplemented below.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

As stated in the previous Office Action, the claims are genus claim that is directed toward a genus of inteins; a genus of split inteins; a genus of split inteins derived from RecA, DnaB, PspPol-I, or Pfu inteins; a genus of split inteins derived from SspDnaE. The scope of each genus includes many members with widely differing structural, chemical, and physiochemical properties. Furthermore, each genus is highly variable because a significant number of structural differences between genus members exists.

The specification discloses modified polynucleotides encoding modified Ssp DnaE N-intein and modified Ssp DnaE C-intein and their use in the preparation of modified enzymes including cyclic dihydrofolate reductase and cyclic pseudostellarin F. However, the specification fails to provide a written description of representative members of each claimed genus for which predictability of structure and function can be ascertained.

The disclosure of these polynucleotides is insufficient to be representative of the attributes and features of all species encompassed by the claims. In view of the above considerations, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise,

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and exact terms that a skilled artisan would recognize Applicants were in possession of a genus of inteins; a genus of split inteins; a genus of split inteins derived from RecA, DnaB, PspPol-I, or Pfu inteins; a genus of split inteins derived from SspDnaE.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-11 stand rejected under 35 U.S.C. 102(b) as being anticipated by Holford et al. (Structure. 1998 Aug 15;6(8):951-6; PTO 1449 filed 6/15/2001).

Applicants' arguments filed 11/18/2005 have been fully considered but are not persuasive. Applicants' position is that Holford et al. do not teach the intein taught by applicants but rather teach the introduction of an N-terminal cysteine and a C-terminal thioester which allows for an intra molecular ligation. The examiner respectfully disagrees for reasons of record as supplemented below.

As stated in the previous Office action, the specification defines the word "intein" as a polypeptide sequence that can catalyze a splicing reaction during post-translational processing of a protein (see p. 13, lines 3-5). As stated in the previous Office Action, Holford et al. teach the concept of how head-to-tail cyclized recombinant peptides and proteins could be made using the taught Expressed Protein Ligation (EPL) and nucleic acids encoding, where introduction of an N-terminal cysteine and a C-terminal thioester within the same polypeptide chain allows for intramolecular native chemical ligation; and that this process has been used to prepare synthetic circular protein domain (see entire document, especially p. 955, penultimate paragraph).

Thus, when the teachings Holford et al. are read in view of this definition of "intein" stated by the specification, the N-terminal polypeptide sequence of the recombinant protein containing the introduced N-terminal cysteine is deemed to be the first portion of a split intein; the C-terminal polypeptide sequence containing the introduced C-terminal thioester is deemed to be the second portion of a split intein; and the polypeptide sequence in between is deemed to be the target peptide that is to be cyclized.

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It is clear from the claims as written that the teachings of Holford et al. do anticipate the claimed invention. The claims as written do not specifically state that the N- and C-terminal inteins are separate and distinct proteins that actually associate to form a complex that initiates and drives the cyclization reaction as argued by applicants. The claims as written do not specifically exclude the introduction of a cysteine and thioester as taught by Holford et al. as argued by applicants.

Thus, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 U.S.C. § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claims 14-40 and 53-89 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Guan et al. (US Patent 5,643,758) in view of Holford et al. (Structure. 1998 Aug 15;6(8):951-6; PTO 1449 filed 6/15/2001). The teachings of the references and the content of this rejection have been stated in the previous Office action and are reproduced below.

Applicants' arguments filed 11/18/2005 have been fully considered but are not persuasive. Applicants' position is that Holford et al. do not teach the intein taught by applicants and that the reference of Guan et al. does not teach or disclose the use of inteins for the purification of a peptide that has been generated by the methods of the invention. The examiner respectfully disagrees for reasons of record as supplemented below.

As stated above in the rejection of claims 1-11 under 35 U.S.C. 102(b), when the teachings of Holford et al. are read in view the specification's definition of "intein", the N-terminal polypeptide sequence of the recombinant protein containing the introduced N-terminal cysteine is deemed to be the first portion of a split intein; the C-terminal polypeptide sequence containing the introduced C-terminal thioester is deemed to be the second portion of a split intein; and the polypeptide sequence in between is deemed to be the target peptide that is to be cyclized.

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The claims as written do not specifically state that the N- and C-terminal inteins are separate and distinct proteins that actually associate to form a complex that initiates and drives the cyclization reaction as argued by applicants. The claims as written do not specifically exclude the introduction of a cysteine and a thioester taught by Holford et al. as argued by applicants.

MPEP 706.02(j) states the following:

“To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant’s disclosure. In re Vaack, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Guan et al. teach expression vectors, prokaryotic and eukaryotic host cells, and methods for making, expressing, isolating, and purifying any protein fused to the *E.coli* maltose binding protein (MBP) using the said expression vectors, prokaryotic and eukaryotic host cells; and that these methods and products are useful for purifying virtually any hybrid polypeptide molecule employing recombinant techniques (see entire publication of US Patent 5,643,758).

The teachings of Holford et al. have been stated above.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Guan et al. such that the nucleic acid molecules taught by Holford et al. are substituted into the vectors, host cells, and method for making polypeptides taught by Guan et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do this for the purposes of creating a beneficial method for producing cyclic proteins and enzymes. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly *prima facie* obvious.

The examiner has determined the scope and contents of the prior art, ascertained the differences between the prior art and the claims at issue, and found the claimed invention to have been obvious in light of the combined teachings of the references.

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Conclusion

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF


TEKCHAND SAIDHA
PRIMARY EXAMINER